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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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10/659,036

09/09/2003

David J. FitzGerald

015280-361200US

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09/19/2006

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EXAMINER

BOESEN, AGNIESZKA

ART UNIT

PAPER NUMBER

1648

DATE MAILED: 09/19/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/659,036

Applicant(s)

FITZGERALD ET AL.

Examiner

Agnieszka Boesen

Art Unit

1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 07 July 2006.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-11 is/are pending in the application.
- 4a) Of the above claim(s) 8-11 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-7 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SB/08)  
Paper No(s)/Mail Date 7/7/06.

- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

This Non-Final Office Action is responsive to the communication received July 7, 2006.

#### ***Election/Restrictions***

Applicant's election of group I, claims 1-7, is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement with respect to any other groups, the election has been treated as an election without traverse (MPEP § 818.03(a)). Thus, the restriction is deemed proper and is made FINAL.

Claims 8-11 are withdrawn because the claims are drawn to the non-elected invention.

Claims 1-7 are pending and under examination.

#### ***Priority***

Acknowledgment is made for priority to a CIP application, 09/462,713, which is a 371 of PCT/US98/14336, which claims benefit of 60/056,924.

#### ***Information Disclosure Statement***

An initialed and dated copy of Applicant's IDS form 1449 is attached to the instant Office action.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

**Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement.** The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The instant invention is drawn to a method of eliciting IgA-mediated immune response in a subject comprising administering a non-toxic exotoxin A-like chimeric immunogen comprising a cell recognition domain of between 10 and 1500 amino acids, a translocation domain, a foreign epitope domain of between 5 and 1500 amino acids and an ER retention sequence.

The instant specification provides written description for a PE-like chimeric immunogen, which contains the *Pseudomonas* exotoxin Ia domain, the II domain, the III domain and a portion of the Ib domain including an insertion of the HIV-1 envelope V3 loop comprising between 14-26 amino acids. The specification has not described substitutions comprising up to 1500 amino acids in the exotoxin A-like chimeric immunogen that would maintain the translocation function of domain II and the ER retention signal of domain III. The specification does not provide written description of a foreign epitope domain of between 5 and 1500 amino acids.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus.

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The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of a number of amino acids, between 10 and 1500 that are comprised within the cell recognition domain and the number of amino acids that, between 5 and 1500, that comprise a foreign epitope. There is not even identification of any particular portion of the structure that must be conserved. It is not known which cell recognitions domains and which foreign epitopes will retain the ability to perform the claimed function such as binding to the cell and induction of an immune response, while the amino acid number can vary so drastically. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

[*Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required.

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See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

From the disclosure one of ordinary skill in the art would not recognize that Applicant was in possession of the full scope of the invention as set out in claim 1. Therefore, the instant invention is not supported by a sufficient written description.

**Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a PE-like chimeric particle that has the V3 loop substituted between the cysteines in the Ib region, does not reasonably provide enablement for a 1500 aa cell recognition domain and a 1500 aa foreign epitope domain while maintaining essential structures required for the functions of domains II and III.**

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims. The instant specification provides an example of using the exotoxin A-like chimera as an immunogen at various inoculation sites and showing that it is able to stimulate an IgA response. The PE-like particle contains the exotoxin Ia domain, the II domain, the III domain and a portion of the Ib domain has been replaced with the HIV-1 envelope V3 loop comprising between 14-26 amino acids. The specification has only taught how to make an immunogen with a small substitution in the Ib domain, which is not significantly larger in size than the native Ib sequence. Neither the specification nor the prior art have shown to how make two simultaneous substitutions comprising up to 1500 aa each in a PE-like chimeric immunogen that would maintain the translocation function of domain II and the ER retention signal of domain III.

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There are several issues that arise when making large insertions, especially two large insertions, into the same protein. How do these insertions affect each other through intramolecular bonding? This interaction cannot be predicted based on the specification or the art in general. These intramolecular bondings could lead to the loss of essential epitopes. What effect would there be on the folding of domain II and domain III? Protein folding is very sensitive to even minor alterations in the sequence (Grigera et al. Immunogenicity of an Aphotavirus chimera of the glycoprotein of Vesicular Stomatitis Virus, Journal of Virology, Vol. 70, p. 8492-8501) and adding two 1500 aa acid inserts would certainly be substantial. Adding an alternate cell recognition domain would also raise issues as to whether this recognition domain by its sheer bulk would block access to the foreign epitope site located in the Ib region even for small epitopes, like the V3 loop region disclosed in the specification. It is also not clear if all the epitopes have to be loops in order to be displayed properly in the Ib region. In case the non-native epitope comprises multiple epitopes, it is not known how the intracellular processing of the immunogen would affect particular single epitopes. In case that the proteasome cleavage would result in loss of the intact epitope, the claimed immunogenic property of the chimera would be lost. The specification provides insufficient guidance with regard to these issues and provides only a limited working example that does not provide sufficient guidance to one skilled in the art to predict the potential folding and presentation of the foreign epitopes. No evidence has been provided which would allow one of skill in the art to predict the efficacy of the claimed method outside of the scope presented in the specific examples with reasonable expectation of success. For the above reasons, it appears that undue experimentation would be required to

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practice the claimed inventions with a reasonable expectation of success. Therefore, the claimed invention is not enabled in its full scope.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

**Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cryz et al. (Vaccine, 1995) in view of Bukawa et al. (Nature Medicine, 1995) as evidenced by Cryz et al. (Infection and Immunity, 1986).**

The claims are drawn to a method of eliciting a secretory IgA-mediated immune response in a subject comprising administering, to at least one mucosal surface, *Pseudomonas* exotoxin A-like chimeric immunogen comprising a foreign epitope, wherein the epitope comprises a V3 loop apex of HIV-1.

Cryz (Vaccine, 1995) teaches a method of eliciting an immune response by administering *Pseudomonas* exotoxin A-like chimeric immunogen comprising a V3 loop apex of HIV-1 epitope, which is also called a principal neutralizing determinant PND (see the entire document, particularly page 67 and Materials and Methods). Cryz (Vaccine, 1995) does not expressly teach that exotoxin A is derived from *Pseudomonas*, but refers to another reference by Cryz (Infection and Immunity, 1986) discussing purification of exotoxin A from *Pseudomonas*.



Cryz (Vaccine, 1995) teach administration of the chimeric immunogen by intramuscular route and generation of IgG antibodies against the immunogen but Cryz does not teach administering Pseudomonas exotoxin A-like chimeric immunogen to mucosal surfaces. Bukawa teaches mucosal administration of a chimeric immunogen comprising cholera toxin and HIV-1 derived foreign epitope. Administration of Bukawa's chimeric immunogen results in generation of IgA-mediated immune response (see the entire document).

It would have been obvious to the person of ordinary skill in the art to administer Pseudomonas exotoxin A-like chimeric immunogen comprising an epitope derived from V3 loop apex of HIV-1 to mucosal surfaces to elicit IgA-mediated immune response.

One would have been motivated to administer the immunogen taught by Cryz to mucosal surfaces as taught by Bukawa, because Bukawa teaches that control of pandemic infection of HIV-1 requires means of developing mucosal immunity against HIV-1 because sexual transmission of the virus occurs mainly through mucosal tissues.

One would have had a reasonable expectation of success of inducing IgA-mediated immune response by mucosal administration of the chimeric immunogen because Bukawa's chimeric immunogen comprising cholera toxin and HIV-1 derived epitope has been successfully used to elicit IgA-mediated immune response when administered by mucosal route.

### ***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Agnieszka Boesen whose telephone number is 571-272-8035. The examiner can normally be reached on 9:00 AM to 5:30 PM.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

AB

Agnieszka Boesen, Ph.D.  
Examiner

9114106

*Stacy B. Chen 9/14/06*  
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PRIMARY EXAMINER